Review of Pathological Hallmarks of Schizophrenia: Comparison of Genetic Models With Patients and Nongenetic Models

Hanna Jaaro-Peled[2], Yavuz Ayhan[2], Mikhail V. Pletnikov[2], and Akira Sawa[1,2]

[2]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287

Schizophrenia is a condition that impairs higher brain functions, some of which are specific to humans. After identification of susceptibility genes for schizophrenia, many efforts have been made to generate genetics-based models for the disease. It is under debate whether behavioral deficits observed in rodents are sufficient to characterize these models. Alternatively, anatomical and neuropathological changes identified in brains of patients with schizophrenia may be utilized as translatable characteristics between humans and rodents, which are important for validation of the models. Here, we overview such anatomical and neuropathological changes in humans: enlarged ventricles, dendritic changes in the pyramidal neurons, and alteration of specific subtypes of interneurons. In this review, we will overview such morphological changes in brains from patients with schizophrenia. Then, we will describe that some of these alterations are already recapitulated even in classic nongenetic models for schizophrenia. Finally, in comparison with the changes in patients and nongenetic models, we will discuss the anatomical and neuropathological manifestation in genetic models for schizophrenia.

Key words: brain imaging/ventricular enlargement/ neuropathology/interneurons/spine density

Introduction

SZ is a condition that impairs high brain functions, some of which are specific to humans, complicating modeling the disease in mice. How can we evaluate in mice the existence of hallucination, delusion, and disorganized speech, which are characteristics of schizophrenia? Thus, behavioral deficits observed in mouse models might not serve as sufficient criteria to judge whether they are good models for schizophrenia.

For the past decade, there has been enormous progress in understanding the neurobiology of schizophrenia.[1] Major progress was made by identification of susceptibility genes for schizophrenia.[2] Although causality is hard to prove, these genetic factors have shed light on specific biological cascades that are linked to the pathology of the disease.[3] Another major advance in schizophrenia research is identification of structural and pathological alterations that are frequently found in brains of patients with schizophrenia: Enlarged ventricles at the gross anatomy level have been reported in many brain imaging studies[4]; dendritic changes in the pyramidal neurons[5] and alteration of specific subtypes of interneurons[6] are known to be important in the pathology of schizophrenia.

Mouse models for other brain disorders, such as Alzheimer disease, have been validated by utilizing representative neuropathological hallmarks found in the brains from patients with these diseases.[7] As a result, these models are accepted to be very useful for molecular understanding of the mechanisms and course of the disease, as well as promising for compound screening for translational purposes. Combined with the ability to modulate the etiology of disease directly by straightforward genetic engineering, mice provide a good resource for modeling brain disorders. In analogy to these successful cases, anatomical and neuropathological changes identified in brains of patients with schizophrenia may become good indicators to validate possible mouse models for schizophrenia.

Based on this notion, this review first summarizes anatomical and neuropathological changes in schizophrenia brains that have been reported in brain imaging and neuropathological studies. We then discuss how such hallmarks are studied in putative mouse models for schizophrenia. In this discussion, we will also overview neuropathological changes found in classic nongenetic rodent models for schizophrenia, although most of them have been generated in rats. Compared with nongenetic models, we will finally discuss how genetically engineered mice will be useful in studies of schizophrenia with both basic and translational significance. This

[1]To whom correspondence should be addressed; tel: 1-410-9554726, fax: 410-6141792, e-mail: asawa1@jhmi.edu.

Table 1. Structural and Morphological Abnormalities in Schizophrenia Patients. (meta, meta-analysis; *, first episode)

	Brain Region	Representative References
Gross anatomy (imaging)		
Decreased brain volume	Whole brain	Vita et al[8] meta*, Steen et al[10] meta*, Wright et al[9] meta
	Temporal lobe	Shenton et al[4] review
	Hippocampus	Vita et al[8] meta*, Steen et al[10] meta*, Wright et al[9] meta
	Amygdala	Wright et al[9] meta
	Thalamus	Ellison-Wright et al[11] meta*
	Anterior cingulate	Ellison-Wright et al[11] meta*
	Basal ganglia-thalamocortical circuit	Ellison-Wright et al[11] meta*
Enlarged ventricles	Lateral ventricles	Vita et al[8] meta*, Steen et al[10] meta*, Shenton et al[4] review, Wright et al[9] meta
	Third ventricles	Vita et al[8] meta*, Shenton et al[4] review
Changed asymmetry		Sommer et al[19] meta
Decreased white matter	Whole brain	Wright et al[9] meta
	Frontal & temporal cortex	Ellison-Wright 2009 meta
Neurohistology		
Pyramidal neurons		
Reduced neuron density	PFC (no change in cell number	Selemon and Goldman-Rakic[20] review
Reduced soma size	PFC	Rajkowska et al[21]
Reduced dendritic field	PFC	Black et al[22]
Reduced spine density	FC	Glantz and Lewis[5]
Interneurons		
Less GAD67+	PFC (mRNA)	Akbarian et al[26]
Less reelin+	PFC (mRNA)	Guidotti et al[23]
Less parvalbumin+	PFC (IR)	Beasley et al[28]
	Hc (IR)	Zhang and Reynolds[30]
No change in calretinin+	PFC (IR)	Beasley et al[28]
	Hc (IR)	Zhang and Reynolds[30]
Less somatostatin+	PFC (mRNA)	Hashimoto et al[32]
Less cholecystokinin+	PFC (mRNA)	Hashimoto et al[32]
Glia		
Fewer oligodendrocytes	PFC	Vostrikov et al[35]
	Thalamus	Byne et al[33]
	Hc	Schmitt et al[34]

Note: PFC, prefrontal cortex; IR, immunoreactivity; Hc, hippocampus.

review does not aim at covering all previous publications and models but instead proposes a useful strategy for mouse models for schizophrenia research.

Anatomical and Neuropathological Changes in Schizophrenia Patients

Gross Anatomy by Brain Imaging

Advances in brain imaging technology, especially magnetic resonance imaging, have established that there are significant, although not very robust, anatomical changes in brains of patients with schizophrenia (table 1).

Imaging studies of chronic schizophrenia patients have detected enlarged ventricles (figure 1A) accompanied by volume decreases in amygdala, parahippocampal gyrus, and temporal lobes.[4,8,9] Enlarged lateral and third ventricles and decrease in whole brain, hippocampal, basal ganglia, and thalamic volumes are present in first-episode patients with schizophrenia.[10,11] There has been a debate about how long these changes continue after the onset of the disease. Recent longitudinal studies have suggested continuously progressive decreases in volumes of brain tissue and increases in volumes of lateral ventricles up to at least 20 years after the first symptoms. Progressive volume loss after the onset of the disease seems most pronounced in the frontal and temporal gray matter areas.[12] Focusing on the frontal lobe, progressive volume decreases have been repeatedly reported.[13–15] The progression of cortical gray matter deficits could arise from pathological disease progression, drug effect,[16] or possibly in some cases comorbidity such as alcoholism.[17]

Evaluation of the integrity of white matter fiber tracts by diffusion tensor imaging has shown abnormalities in the prefrontal and temporal lobes, cingulum, and corpus callosum.[18]

The normal human brain is anatomically and functionally asymmetrical. A meta-analysis of anatomical asymmetry in schizophrenia found abnormal brain torque and
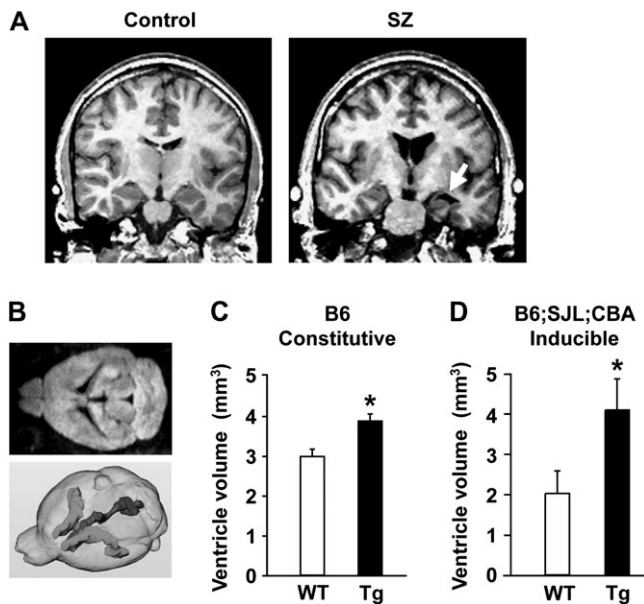
Fig. 1. In Vivo Magnetic Resonance Imaging Demonstrating Enlarged Lateral Ventricles in Both Patients With Schizophrenia and Mouse Models for Schizophrenia. A, Schizophrenia patients: shrinkage in the left temporal horn is detected (white arrow). B–D, mouse models for schizophrenia: a representative 2-dimensional image with the lateral ventricles (top in B) and a 3-dimensional construction (bottom in B). Enlarged lateral ventricles in transgenic mice expressing a truncated, dominant-negative form of *DISC1* (C, conventional model in the C57 black strain; D, inducible model in a mixed genetic background). (A, reprinted with permission from *The New England Journal of Medicine*; 1992; B, top panel, and C, adapted from *Proceedings of National Academy of Sciences United States of America*; B, bottom panel, and D, reprinted by permission from *Molecular Psychiatry;* 2007.

decrease of asymmetry favoring the left planum temporal and left Sylvian fissure. Because asymmetries in these areas are strongly related to cerebral dominance, the decreased temporo-parietal asymmetries may contribute to the decreased language dominance in schizophrenia.[19]

Neuropathology Observations

There are 3 major pathological changes in autopsied brains from patients with schizophrenia. In interpreting the neuropathological data in schizophrenia brains, it is important to be aware of the existence of confounding factors, in particular long-term medication.

Pyramidal Neurons. The volume changes detected by brain imaging may be explained, at least in part, by dense packing of neurons in the cortex. Morphometric analyses of the prefrontal cortex (PFC) have revealed increased density of pyramidal cells in schizophrenia brains, without alteration in total cell numbers.[20,21] The more dense packing of neurons may occur due to decreased soma size and decreased neuropil, and evidence exists for both. These 2 factors are actually related because there is a correlation between soma and dendritic arbor size. The soma

of pyramidal neurons in the PFC is smaller in schizophrenia brains compared with that in normal controls.[20] The dendrites are shorter and less branched in schizophrenia.[22,23] Furthermore, the spine density is lower in schizophrenia (figure 2A).[5,24] These neuropathological changes may underlie a disturbance in neuronal connectivity in schizophrenia.

Interneurons. For the past decade, many groups have reported molecular changes associated with interneurons in the cortex. An unbiased approach to examine gene expression profile by microarray analysis suggested the presence of molecular changes in γ-aminobutyric acid (GABA)–producing (GABAergic) neurons.[25] More specifically, decrease in a GABA-synthesizing enzyme, glutamic acid decarboxylase-67 (GAD67), has been reproducibly observed.[23,26,27] Reduction of calcium-binding proteins that are selectively expressed in subclasses of GABAergic interneurons in the PFC and hippocampus, such as parvalbumin and calbindin, has been reported (figure 3A).[6,28–30] No changes have been found in the expression of the third class of calcium-binding proteins, calretinin. The parvalbumin-positive neurons are of special interest because they are fast spiking, synchronize pyramidal neuron firing, and give rise to the gamma oscillations, which are impaired in schizophrenia (reviewed in Lewis).[31] Decrease in the expression of the neuropeptides, somatostatin, and cholecystokinin suggests that GABA neurotransmission is impaired in the Martinotti and non–fast-spiking basket cell subsets of GABAergic neurons as well.[32]

Oligodendrocytes. Fewer oligodendrocytes in various brain regions have been reported in schizophrenia.[33–35] In addition, a series of gene expression studies have indicated that expression levels of myelin-related genes are decreased in schizophrenia. The most notable result of a genome-wide expression analysis of postmortem dorsolateral frontal cortex was downregulation of 5 oligodendrocyte-enriched genes that are involved in myelination.[36] Another study, which focused a priori on oligodendrocyte-specific and myelination-associated genes in PFC, found a downregulation of key oligodendrocyte and myelination genes, including transcription factors that regulate these genes.[37] These alterations may underlie or explain white matter deficits found in some brain imaging studies, contributing to the pathology of neuronal disconnectivity in schizophrenia.[38]

Structural and Anatomical Changes in Nongenetic Rodent Models of Schizophrenia

Many investigators attempted to generate models for schizophrenia even before identification of genetic susceptibility factors for schizophrenia in the past decade. Most of the efforts have been made with rats, not with
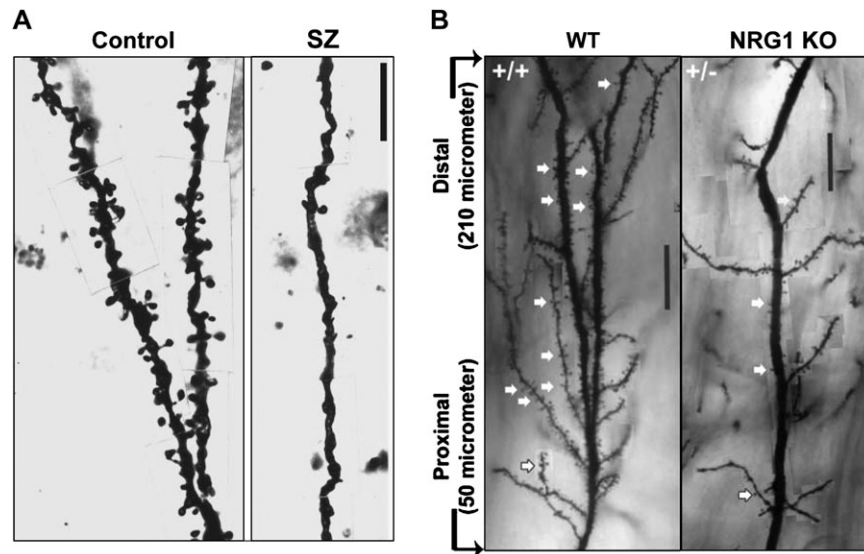
Fig. 2. Decrease in Dendritic Spine Density in Both (A) Patients With Schizophrenia (Prefrontal Cortex) and (B) A Mouse Model for Schizophrenia (Neuregulin-1 Type III Knockout Mice Compared With Wild-Type Animals in Hippocampus). (A, Adapted from *Archives of General Psychiatry*; 57:65–73; B, with permission from Chen et al[73] *Journal of Neuroscience*; 2008).

mice. Such an approach is divided into 3 key strategies: the first approach is to focus on the pathophysiology of the disease, without considering its real etiologies and pathological course. Animals treated with drugs that can elicit psychotic symptoms in humans are used in this category of models. The second approach is to use environmental stressors that may play roles in the path-

ological course of schizophrenia. As described below, prenatal/perinatal complications and postnatal stress can elicit, in addition to behavioral deficits in adulthood, some neuropathological traits in rodents similar to those reported in brains of schizophrenia patients. The third approach is to emphasize the neurodevelopmental risks of schizophrenia in general and to make brain lesions
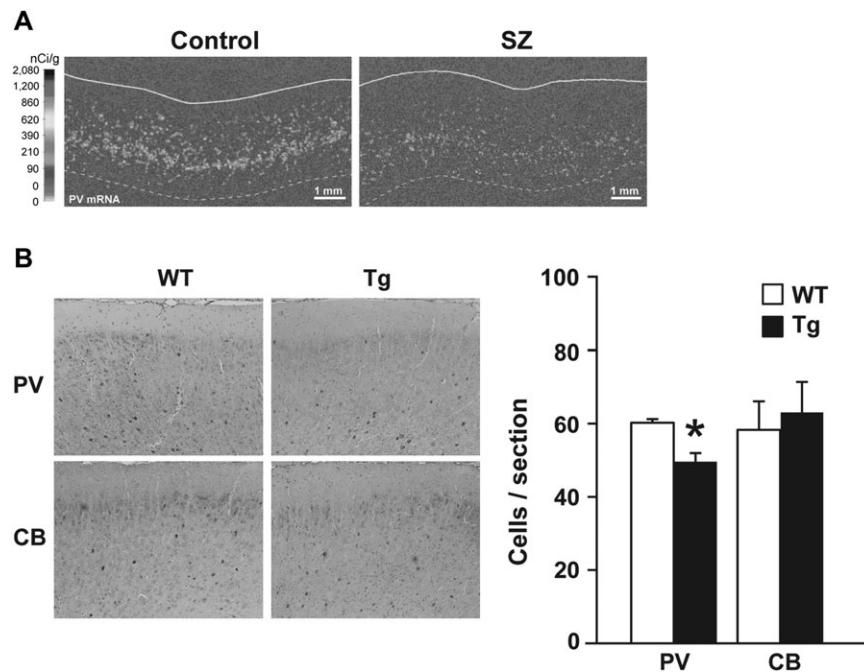

Fig. 3. Decrease in the Level of Parvalbumin (PV) Expression in the Prefrontal Cortex, Observed Both in (A) Schizophrenia Patients (mRNA Level) and (B) A Mouse Model for Schizophrenia (disrupted in schizophrenia-1 [DISC1] Transgenic Mice Expressing the Truncated, Dominant-Negative Form of "DISC1"). There was decrease in PV staining but not in calbindin (CB) staining. A, reprinted by permission from *Nature Reviews Neuroscience*[31]; 2005. B, adapted from *Proceedings of the National Academy of Sciences United States of America*.[81]

at appropriate timing by using toxins. Here, we cover the most representative models from each category (table 2).

Pharmacological Models

N-Methyl-D-Aspartic Acid Receptor Antagonists. Exposure of humans to *N*-methyl-D-aspartic acid (NMDA)–type glutamate receptor antagonists, such as phencyclidine (PCP), causes schizophrenia-like symptoms.[39] Thus, this drug has been administered also to rodents, attempting to build a model for schizophrenia. In rodents treated subchronically with PCP in adulthood, in addition to behavioral manifestations similar to the endophenotypes of schizophrenia,[40] an important histological trait in human schizophrenia has been reproduced: decreased parvalbumin in the PFC (in mice)[41] and the hippocampus (in rats).[42] Furthermore, subchronic PCP treatment of rats decreases the number of synaptic spines in the PFC, detected by electron microscopy.[43] The same article reported increased density of astrocyte processes without change in the number of astrocytes in PCP-treated rats, which has not been reported in schizophrenia patients. Taken together, signs of interneuron deficits and synaptic spine changes support the idea that PCP induces, at least in part, schizophrenia-like pathophysiology. At present, the subchronic PCP model is widely used, especially in compound screening for schizophrenia treatment. In addition to PCP, treatment with other NMDA receptor antagonists also results in schizophrenia-like pathophysiology. For example, chronic administration of ketamine in rats reduces the density of parvalbumin-immunoreactive hippocampal interneurons.[44] Chronic MK-801 treatment in rats has a similar effect in the hippocampus: decreased immunoreactivity of parvalbumin without change in that for calretinin but no effect in the PFC.[45]

Amphetamine. Amphetamine can mimic mainly the positive symptoms of schizophrenia by increasing the dopamine concentration in the synaptic cleft.[46] Escalating amphetamine injection results in decreased GAD67 immunoreactivity in the hippocampus, PFC, thalamus, and amygdala. This was not accompanied by enhanced neurotoxicity or reactive gliosis.[47]

Environmental Stress Models

Prenatal/Perinatal Environmental Insults. Prenatal/antenatal environmental insults, especially birth hypoxia and congenital virus/pathogen infection, are well-established environmental risk factors for schizophrenia.[48] Maternal infections, especially during the first and second trimester increase the risk for schizophrenia. It still remains debatable whether and/or why infection at certain gestation periods may confer maximal risk for neurodevelopmental disturbances.[49] A rat model of delayed cesarean section shows decreased spine density of the pyramidal neurons of the PFC and the hippocampal cornus ammonis 1 (CA1) at postnatal day 35 (P35). When Cesarean section is combined with anoxia, the decrease in spine density of the PFC is further augmented. Increase in the length of dendrites of medium spiny neurons is also observed at P35 but is normalized by P70.[50] Injection of double-stranded RNA polyinosinic-polycytidylic acid (Poly I:C) mimics the immune response elicited by viral infection. Poly I:C injection to a mouse dam around gestational day 9 (G9, late first trimester) results in decreased myelination and axonal diameters in the hippocampus of juvenile offspring, without loss of oligodendrocytes.[51] Immunohistochemistry for the GABA$_A$ receptor α2 subunit detects increases in the ventral (but not in the dorsal) dentate gyrus and basolateral amygdala in adult offspring after poly I:C at G9.[52] Infection of mice with influenza virus at G9 results in increased pyramidal and nonpyramidal cell densities and increased brain size in offspring in adulthood.[53] When the influenza infection is carried out in the late second trimester (G18), the offspring display smaller brain volume and fractional anisotropy of the corpus callosum, as well as white matter atrophy at P35.[54] Prenatal challenge with the bacterial immune activator lipopolysaccharide in rats reduces the dendritic arbor and spine density in the medial PFC and CA1 pyramidal neurons and affects spine structure at CA1.[55]

Postnatal Stress. Rats normally live in social groups. When reared in isolation after weaning, various neurobehavioral abnormalities emerge. The following behavioral abnormalities have been reported: volume loss of the medial PFC without change in neuron number,[56] as well as decreased dendritic spine density on PFC and hippocampal pyramidal neurons with reduced dendritic length only at the hippocampus.[57] Stress can be mediated by corticosteroids. Thus, chronic corticosteroid treatment in rats results in neuronal loss and atrophy specifically of layer II of the infralimbic, prelimbic, and cingulate cortices.[58]

Developmental Lesion Models

Neonatal Hippocampal Lesion. A classic neurodevelopmental schizophrenia model is generated by excitotoxic lesion of the ventral hippocampal formation in rats at P7.[59] When analyzed in adulthood, the basilar dendrites of the PFC layer 3 pyramidal neurons are shorter and less branched and have decreased spine density, similar to findings from schizophrenia patients.[60] GAD67 mRNA is decreased in the PFC in these rats implying a deficit in GABAergic interneurons.[61]

Methylazoxymethanol. Administration of a mitotoxin, methylazoxymethanol (MAM), to pregnant rats interferes with development of the embryonic brain region in which progenitor cells proliferate.[62] When administered once

Table 2. Structural and Morphological Abnormalities in Nongenetic Rodent Schizophrenia Models (Poly I:C, Polyinosinic-Polycytidylic Acid; PCP, Phencyclidine; BLA, Basoleteral Amygdala; DG, Dentate Gyrus; GFAP, Glial Fibrillary Acidic Protein; Hc, Hippocampus; IR, Immunoreactivity; mPFC, Medial Prefrontal Cortex)

Model	Imaging	Neuropathohistology				
		Gross Anatomy	Cytoarchitecture	Pyramidal Neurons	Interneurons	Glia
N-methyl-D-aspartic acid receptor antagonists						
PCP (rat)				Fewer PFC synapses (Hajszan et al[43])	Less parvalbumin + IR in Hc (Jenkins et al[42])	Increased astroglia process density w/o change in glia number (Hajszan et al[43])
PCP (mouse)					Fewer parvalbumin + mRNA cells in PFC (Thomsen et al[41])	
Ketamine (rat)					Fewer parvalbumin + IR cells in Hc (Keilhoff et al[44])	
MK-801 (rat)					Less parvalbumin + IR, no change in calretinin in Hc (Braun et al[45])	
Dopamine enhancement						
Amphetamine (rat)					Reduced GAD67 IR in Hc, PFC, thalamus, amygdala (Peleg-Raibstein et al[47])	No change in GFAP in caudate-putamen (Peleg-Raibstein et al[47])
Prenatal/perinatal environmental insults						
Cesarean +/− anoxia (rat)				Changes in spine density and dendrite length at the PFC and CA1 (Juarez et al[50])		
Poly I:C (mouse G9)		Decreased Hc myelination (Makinodan et al[51])			Increased GABAA α2 IR at ventral DG and BLA (Nyffeler et al[52])	No change in oligodendrocyte number (Makinodan et al[51])
Influenza (mouse G9)		Enlarged brain (Fatemi et al[53])	Increased pyramidal and nonpyramidal cell density (Fatemi et al[53])			Increased GFAP IR in cortex and Hc (Fatemi et al[53] Mol)
Influenza (mouse G18)	Smaller brain volume, white matter atrophy at the corpus callosum (Fatemi et al[54])					

Table 2. Continued

| Model | Imaging | Neuropathohistology | | | | |
		Gross Anatomy	Cytoarchitecture	Pyramidal Neurons	Interneurons	Glia
LPS (rat G15–16)				Reduced dendrite length and spine density in mPFC and CA1 (Baharnoori et al[55])		
Postnatal stress						
Isolation rearing (rat)		Smaller mPFC w/o change in cell number (Day-Wilson et al[56])		Reduced dendritic length at CA1 and decreased spine density at mPFC, Hc (Silva-Gomez et al[57])		
Chronic corticosteroids (rat)			Neuronal loss and atrophy of PFC layer2 (Cerqueira et al[58])			
Developmental lesions						
Neonatal Ventral Hc (rat)				Shorter and less branched basilar dendrites and reduced spine density at the mPFC (Flores et al[60])	Decreaced GAD67 at the PFC (Lipska et al[61])	
MAM (rat)		Thinning of the entorhinal cortex, abnormal temporal asymmetry (Talamini et al[63])	Disorganized cortical layering (Talamini et al[63])		Decreased density of parvalbumin neurons at the mPFC, Hc (Lodge et al[64])	

during gestational days 9–12 (G9–12), the entorhinal cortex shows cortical thinning, disorganized cortical layering, and abnormal temporal asymmetries.[63] The abnormalities are more evident the later the lesion. When MAM is administered at G17, adult offspring display decreased density of parvalbumin-positive interneurons at the medial PFC and ventral subiculum of the hippocampus.[64]

Structural and Anatomical Changes in Genetic Mouse Models of Schizophrenia

Schizophrenia susceptibility genes identified by human genetic studies have been found only recently, finally enabling generation of mouse models on the basis of genetic etiology. Because causal mutations per se have not been identified, there is still debate on the significance of each gene. Nonetheless, many of the genetically engineered models for these genes display behavioral abnormalities and morphological/anatomical alterations that may be relevant to schizophrenia. Here, we discuss morphological/anatomical changes in these mice. Among promising candidate genes for schizophrenia, as far as we are aware, no mouse models for regulator of G protein signaling 4 and carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase have been published yet. In knockout (KO) mice deficient in neuronal nitric oxide synthase, serine racemase, calcineurin, and metabotropic glutamate receptor, published data do not include anatomical and morphological assessment.[65–69] Thus, in this section, we will introduce genetic models for dysbindin, neuregulin-1 (NRG1), ErbB4, disrupted in schizophrenia-1 (DISC1), Akt1, and genes found in chromosomal region 22q11 (table 3).

Dysbindin

"Sandy" mice have a spontaneous mutation in the schizophrenia susceptibility gene dysbindin. Because of this mutation, the homozygotes do not express dysbindin protein.[70] These mice have morphological changes in excitatory asymmetrical synapses on hippocampal CA1 dendritic spines: presynaptically bigger but fewer glutamatergic vesicles, narrower synaptic cleft, and broader postsynaptic density.[71] Dysbindin is involved in neurotransmitter release, which may account for the various abnormal behaviors displayed by the Sandy mice.[72]

Neuregulin-1 and ErbB4

Both NRG1 and one of its receptors, ErbB4, are strongly implicated in schizophrenia.[3] Many mouse models with manipulated expression levels of the different NRG1 isoforms have been generated. Adult heterozygous mice with a targeted disruption for type III NRG1 have enlarged lateral ventricles and decreased density of dendritic spines on hippocampal pyramidal neurons (figure 2B). Interestingly, in vivo imaging detected hypo-

function in the medial PFC and hippocampus, and behavioral analysis found cognition-related abnormalities.[73] NRG1 type III is essential for myelination in the peripheral nervous system, but surprisingly conditional KO of NRG1 in cortical projection neurons from embryonic day 12 (E12) or postnatally and double KO of ErbB3/4 result in normal myelination in the central nervous system.[74] Interestingly, transgenic overexpression of NRG1 results in hypermyelination.[74] Mice lacking both ErbB2 and ErbB4 specifically in the central nervous system from early embryonic stages have normal brain morphology but decreased spine density in the cortex and hippocampus. The decreased spine density is expected to disturb the function of neuronal circuits, and indeed, ErbB2/4 KO displayed increased aggression and a PPI deficit.[75] ErbB4 KO display reduced density of parvalbumin-positive cells in the hippocampus, resulting in reduced power of kainate-induced gamma oscillations,[76] as well as reduced density of calbindin-positive and GABAergic interneurons in the cortex.[77] Expression of dominant-negative ErbB4 in oligodendrocytes and myelinating Schwann cells from E15 results in thinning of the myelin sheath of the corpus callosum, altered oligodendrocyte morphology, and a surprising increase in the number of cells expressing a differentiated oligodendrocyte marker. It was suggested that the dopaminergic abnormalities seen in these mice mice might result from the defective myelin.[78]

Disrupted in Schizophrenia-1

Most DISC1 mouse models are based on the fact that the *DISC1* gene was originally identified as truncated by a translocation that segregated with psychiatric diseases. Although there is debate whether such truncated DISC1 product exists at protein levels, the putative truncated protein acts as dominant negative.[79] Thus, regardless that the Scottish genetic mutation results in haploinsufficiency or dominant-negative mutant effect or both, an overall defect is postulated to be a partial loss of DISC1 function.[80] Based on this idea, several transgenic models expressing this truncated protein have been generated.[81–83] Very interestingly, a major common phenotype observed in these transgenic mice is enlarged lateral ventricles, an important hallmark for schizophrenia.[81–83] In addition, in a transgenic mouse expressing truncated DISC1 generated using a bacterial artificial chromosome vector, reduced cortical thickness and partial agenesis of the corpus callosum are also observed.[83] Postnatal expression of this mutant DISC1 in a set of cells in the forebrain may be sufficient to lead to enlargement of lateral ventricles, which has been indicated by 2 types of transgenic mice under the temporal and spatial control by the α-calmodulin kinase II promoter.[81,82] In addition, reduced brain volume is also found in mice with missense mutations L100P or Q31L of DISC1.[84] Another important hallmark for schizophrenia is reduced

Table 3. Structural and Morphological Abnormalities in Genetic Schizophrenia Models

Model	Imaging	Neuropathohistology				
		Gross Anatomy	Cytoarchitecture	Pyramidal Neurons	Interneurons	Glia
Dysbindin				Morphological changes in asymmetrical synapses in CA1 (Chen et al[71])		
NRG1		Increased lateral ventricles (Chen et al[71]), Normal myelin (Brinkmann et al[74])		Reduced spine density in Hc (Chen et al[71], Barros et al[75])		
ErbB4		Normal myelin (Brinkmann et al[74])		Reduced spine density in cortex, Hc (Barros et al[75])	Reduced parvalbumin IR (Fisahn et al[76]) Reduced calbindin IR (Flames et al[77])	Increased oligodendrocyte number, thinner myelin (Roy et al[78])
Disc1	Smaller brain volume, Enlarged lateral ventricles (Hikida et al[81], Pletnikov et al)	Enlarged lateral ventricles partial agenesis of corpus callosum, thinner cortex (Shen et al[83])	Altered organization of dentate granule cells (Kvajo et al[86])	Shorter dendrites (Pletnikov et al, Li et al[85], Shen et al[83])	Reduced parvalbumin IR at mPFC, Hc (Hikida et al[81], Shen et al[83])	
Akt-1				Altered pyramidal cell morphology at PFC (Lai et al[87])	No change in parvalbumin and calbindin density in the PFC (Lai et al[87])	
Δ22q11 (COMT, GNB1L, PRODH, ZDHHC8)				Decreased spine density and dendritic complexity (Mukai et al[89])		

Note: CA1, cornus ammonis 1; DISC1, disrupted in schizophrenia-1; Hc, hippocampus; IR, immunoreactivitiy; mPFC, medial prefontal cortex.

immunoreactivity of parvalbumin.[31] In 2 transgenic mice expressing truncated DISC1, reduced immunoreactivity of parvalbumin is detected in the medial PFC (figure 3B)[81,83] and hippocampus.[83] Abnormalities of hippocampus may underlie the pathophysiology of schizophrenia. In a transgenic model expressing a dominant-negative DISC1 (a C-terminal fragment of DISC1) transiently at P7, reduction of hippocampal dendritic complexity is reported, resulting in reduced hippocampal synaptic transmission.[85] In another type of genetically engineered DISC1 mice, hippocampal granule cells display misorientated and shorter dendrites and decrease in numbers of synaptic spines. These dendritic abnormalities may cause the reduced short-term potentiation at CA3/CA1 synapses and indirectly the working memory deficit found in these mice.[86]

Akt1

Association studies of *Akt1* with schizophrenia have yielded mixed results, but it remains an interesting candidate. Comprehensive morphological analysis of layer V pyramidal neurons in the medial PFC of Akt1 KO reveals mostly normal neuronal densities but abnormal dendritic architecture.[87]

22q11.2

Microdeletion at 22q11.2 causes velocardiofacial syndrome, which consists of congenital abnormalities affecting several tissues and organs. About 25% develop schizophrenia or schizoaffective disorder.[88] Of the many genes in this region, the involvement of *Catechol-O-methyl transferase (COMT)*, *proline dehydrogenase (PRODH)*, *zinc finger*, *DHHC-type containing 8 (ZDHHC8)*, and *guanine nucleotide-binding protein (G protein)*, *beta polypeptide 1-like (GNB1L)* in schizophrenia has been independently supported. A mouse model with a deletion syntenic to the human microdeletion displays decreased density of dendritic spines and decreased dendritic complexity of CA1 pyramidal neurons,[89] which may underlie the prepulse inhibition and fear conditioning deficits in this model.[90]

Perspectives

There is still debate about whether it is possible to use rodents to model psychiatric disorders in which high brain functions that are probably in part unique to humans are impaired. Nonetheless, rodent models, especially genetically engineered mice in which disease-associated etiologies (causal or susceptibility genes) are modified, have potential advantages over human studies. In order to understand disease mechanisms in depth, it is very important to characterize how the disease etiologies develop over time until development of full-blown disease. In the case of schizophrenia, initial risks for the disease occur during neurodevelopment, whereas the disease onset is in young adulthood, with almost 2 decades for the full development of pathology to the onset. Thus, it is very difficult to address this mechanism by human studies. Better understanding of the disease mechanisms and time course, therefore, is expected with use of genetically engineered mouse models. Another major advantage of mouse models is their usefulness for compound screening in drug development. In comparison to primates, rodents are much easier for preclinical drug screening from both economical and ethical viewpoints. Mouse models can provide us with an opportunity to identify novel therapeutic strategies that are directly linked to the disease mechanisms. Mouse models may not be so useful for understanding functions of primate specific schizophrenia candidate genes, such as D-amino acid oxidase activator (*DAOA/G72*).[91]

In this short review, we have tried to establish a series of similarities between pathology in humans (patients with schizophrenia) and rodent models (nongenetic rodent models and genetically engineered mice). It seems clear that the multiple similarities indicate the potential for studying these in more depth, which would provide a firm basis for clarifying the mechanisms underlying some of the characteristics of schizophrenia and useful tools for translation.

Supplementary Material

Color versions of figures 1–3 are available as Supplementary Material at http://schizophreniabulletin.oxfordjournals.org.

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